Groups; Number of Amino Groups; Number of Hydroxyl Groups.

18. A computer-aided method for the provision, identification and description of molecules exhibiting immunomodulatory activity comprising;

a step of molecular modeling in which molecular descriptors of a molecule having immunomodulatory activity are determined computationally;

a step of building a combinatorial library using said molecular descriptors and including molecules having said immunomodulatory activity;

a step of selecting candidate molecules which are potentially immunomodulatory;

a filtering step whereby candidate molecules are filtered using at least one static filter representing a plurality of said molecular descriptors; and

a further filtering step whereby candidate molecules are filtered using at least one dynamic filter representing constraints of conformational variations which each candidate molecule must satisfy in order to exhibit said immunomodulatory activity.

REMARKS

The Examiner notes that the Applicant has not filed a certified copy of the priority application or the PCT application. Applicant has obtained certified copies of both applications and attached them in the accompanying "Submission of Priority Documents" being filed with this Response.

To comply with requirements under 37 C.F.R. §§1.821-1.825, Applicant is resubmitting a sequence listing to correct minor errors in the sequence listing previously submitted. The resubmitted listing contains no new matter. The specification has also been amended to incorporate sequence identifiers thereby bringing the application into compliance with the sequence listing rules.

Regarding the specifications, the Examiner has objected to Table 1 on page 30. Applicant has amended the Table as set forth above. In addition, Applicant has amended page 33, lines 19-24 to reference the proper sequence identifier.

The Examiner has objected to and rejected several claims based on informalities and indefiniteness. Claims 1 and 18 have been amended so as to refer to desired "activity" rather than desired "behaviour" and American spellings employed.

The use of the term "including" when referring to the method steps within claims 1 and 18 has been removed and the steps themselves more clearly linked.

Amended claims 5, 8, 9 and 10 now contain antecedent basis for the term "criteria". Basis for this amendment can be found in part (3) of Claim 3, and in the description of the invention at page 11.

Claim 10 now contains the relevant elements of Table II, and reference to Table II has been deleted.

Claim 18 now explicitly refers to "candidate" molecules.

The Examiner objects to the reference in claims 1 and 18 to "provision" and argues that nothing is provided by the methods defined by those claims. The applicant notes that not only is identification of active molecules provided, a description of such molecules is also provided as is a molecule itself – in a virtual/computational form.

Similarly, the Examiner objects that the term "molecular modelling step" is unclear. Claims 1 and 18 have been amended to explicitly recite that the molecular modeling step of the present invention includes the computational determination of molecular descriptors. It is unreasonable to expect the applicant to restrict the claims

to narrow and specific modeling techniques when the invention is clearly applicable across a wide range of modeling techniques as described within the body of the application. The amended claims now also recite that the step of building a combinatorial library involves using the molecular descriptors derived from the molecular modeling step, thereby more definitely connecting the latter step to the former.

In the final clause of amended claims 1 and 18 (old claims 2 and 69), reference is made to filter-imposed constraints that a molecule must satisfy "in order to exhibit" a desired activity. The claims merely require that candidate molecules satisfy the conditions that are necessary "in order to" enable activity *potentially* to be shown by the molecule. The constraints define necessary molecular conditions for such activity to be at least a potential.

Claim 4 has been clarified to convey that the "enrichment" referred to is an enrichment "in terms of" (i.e. in respect of) the diversity of the molecules (in the combinatorial library) that are associated with the selected molecular descriptors. Molecules may be screened in terms of the degree of enrichment they provide to given molecular descriptors.

Claims 1, 2, 4, 5, 8-10, 18-20 and 69 were further rejected under 35 U.S.C. § 102. Applicant respectfully requests that the Examiner reconsider these rejections. The present invention concerns a methodology for designing a virtual molecule in terms of computationally derived molecular descriptors without it being necessary to synthesise the molecule. Filters are produced which apply constraints to various of the descriptors which define the virtual molecules. The filters define sets of constraints on molecular descriptors which are known to be required of molecules if

those molecules are (potentially) to have a desired activity. Thus, those virtual molecules that pass through given filters have a good chance of being active and may then be synthesised. The filters used are both "static" filters which apply constraints to static molecular descriptors, and "dynamic" filters which apply constraints to dynamic molecular descriptors.

None of the cited documents disclose a dynamic filter representing constraints of conformational variations which *each* candidate molecule must satisfy as required by amended claims 1 and 18. The Examiner has not identified any passages/references to "conformational variations" in any of the cited documents, and the applicant is at a loss to understand what basis the Examiner has for asserting that this feature is not novel.

The meaning of "conformational variations" is defined in detail within the description of the present application as a measure of the range of variations in the shape (i.e. conformation) of a candidate molecule over a period of time. None of the cited prior art refer to a measure being even remotely similar to this. Some of the cited references do not even contain the word "conformation" and those that do contain this word do not refer to the filtering of molecules in terms of conformational "variations", let alone of those variations being in respect of *each* molecule being filtered.

The Examiner claims that the Krieger #1 article (dated February 1996) and the Krieger #2 article (dated September 1996) each disclose a unified method for the provision, identification and description of molecules exhibiting a desired behaviour as defined in the claims of the application subject to examination. The Examiner identifies disjointed passages of text within the Krieger #1 article (one at page 68,

another at page 72) which bear little relation and no reference to each other. No passages are identified in the Krieger #2 article as disclosing relevant method steps, and the Examiner merely asserts anticipation of the present claims thereby. Neither of the two Krieger articles disclose a single unified methodology. Those passages that are identified in Krieger #1 are vague and equivocal anecdotes at best.

For example, Krieger #1 does not disclose any molecular modeling method step in which molecular descriptors are determined computationally as recited in amended claims 1 and 18. The Examiner identifies a passing reference to QSAR at page 69 as disclosing a molecular modeling step within a unified methodology, however this reference to QSAR bears no clear relation to the passages of Krieger #1 previously identified by the Examiner and cannot be seen as part of a unified methodology. Furthermore, it is to be noted that QSAR cannot model a molecular descriptor, it can only model the activity of a molecule but not the molecule/descriptor itself. Consequently, QSAR cannot be said to be a be a molecular modeling step in which molecular descriptors are determined computationally as stipulated in amended claims 1 and 18.

The Examiner refers to a filtering method as identified at column 3 of page 68 of Krieger #1, however this filtering step is clearly applied to a combinatorial library as a whole and not to a candidate molecule as is the case in the present invention as claimed. The filter step of Krieger #1 is performed in order to "reduce [the library] to a specific library" and not to identify an active molecule.

US5463564 (3-D Pharmaceuticals) relates to an iterative process for building a combinatorial library, for selecting molecules from that library, and synthesising molecules from the selected molecules. Lines 12 to 49 of column 17 describe how

structure-activity models, and GFA models are used in this context. The document does not disclose a method for seeking molecules of a desired activity and does not disclose a molecular modeling step in which molecular descriptors are determined computationally. All molecular descriptors are determined experimentally by assay and structure/activity models are constructed from the assay data, not from molecular modeling steps. No descriptors are computed.

Once more, no dynamic filters are disclosed in this document and, therefore, no dynamic filters representing constraints of conformational *variations* upon *each* candidate molecule are disclosed in this document as stipulated by amended claims 1 and 18.

The documents US6185506 (Tripos #1) and US6240374 (Tripos #2) relate to methodologies building a virtual library of molecules in which the molecules are classified using "validated" molecular descriptors. Each "validated" molecular descriptor is chosen such that the number of descriptors used in the library can be reduced without losing the diversity/variation of information available from the (reduced) library. The teaching of these documents is concerned with evaluating "valid" molecular descriptors for use in building a combinatorial library and not with identifying candidate molecules with a desired activity using filters. Filters are not applied to individual candidate molecules in Tripos #1 or #2, and there is no mention of any dynamic filter representing constraints of conformational variations with each candidate molecule.

In conclusion, none of the cited prior art documents contain all of the features of amended Claim 1 and Claim 18 and no unified methodology is disclosed therein which falls within the bounds of amended claims 1 and 18 or any claim dependent

upon them. Consequently, the applicant believes that those claims and the claims which depend from them are both novel and inventive over the cited prior art.

In light of the foregoing, the Applicant believes that this application is in a form for allowance. The Examiner is encouraged to contact the Applicant's undersigned attorney if the Examiner believes that issues remain regarding the allowability of this application.

Respectfully submitted,

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EXHIBIT A

At page 30, lines 1-21, please replace the existing table with the following:

TABLE 1

Peptide sequence	HLA/MHC	MSTSD
untreated		7.5 1.1
RENLRIALRY	B2702	11.4 2.6 (1)
YRLAIRLNER	-	12.1 2.8 (2)
renlrialry	-	11.4 4.1 (1)
yrlairlner	-	13.2 2.7 (2)
RVNLRIALRY	-	11.5 0.5 (3)
YRLAIRLNVR	-	12.5 1.6 (4)
rvnlrialry	-	13.1 3.9 (3)
yrlairlnvr	-	12.2 2.9 (4)
NLRIALRYYW	-	11.6 1.3 (5)
RVNLRTALRY	Kk	8.5 0.7 (6)
RVDLRTLLRY	Dk	7.0 0.5 (7)
RVDKRTLLGY	Kb	7.8 1.0 (8)
RVSLRNLLGY	Db	8.0 0.5 (9)
RESLRLLRGY	07	7.5 0.7 (10)
REDLRTLLRY	B2705	7.7 1.2 (11)
ENLRIALR	-	8.5 0.7 (12)
renlpialry	-	9.5 2.4 (13)
RVNLRTLRRY	E	8.0 0.5 (14)
RMNLQTLRGY	G	7.5 0.7 (15)

*Numbers in parentheses are SEQ ID NOS.

At page 33, lines 19-24, please replace the existing paragraph with the following:

Using the Combex program (Synt:em, Nîmes, France), a combinatorial explosion was generated based on a consensus sequence RXXXRXXXXY (SEQ ID NO: 16), derived from the learning set after aligning all active and inactive sequences. This sequence left seven positions, the positions represented by "X", to mutate in order to create the library.

EXHIBIT B

Additions and Deletions Required of Claims

1. A computer-aided method for the provision, identification and description of molecules exhibiting a desired activity [behaviour, employing] comprising;

a molecular modeling [modelling] step in which molecular descriptors are determined computationally;

a step of building a combinatorial library [building step] of molecules using said molecular descriptors; [and]

a step of selecting [potentially useful] candidate molecules which potentially exhibit said desired activity;

[wherein said method includes] a filtering step whereby candidate molecules are filtered using at least one static filter representing a plurality of said molecular descriptors;

a further filtering step whereby candidate molecules are filtered using at least one dynamic filter representing constraints of conformational variations which each candidate molecule must satisfy in order to exhibit said desired activity.

4. A computer-aided method [for designing molecules] according to Claim 1 further comprising [wherein it further comprises] the step of [:] screening the candidate molecules on the basis of the degree of enrichment [in molecular diversity terms] provided by each candidate molecule to molecular descriptors [in relation to the selected descriptors].

5. A computer-aided method according to Claim 1 further comprising the step

of deriving one or more criteria associating descriptor values with activity, said criteria including at least one static criterion and at least one dynamic criterion wherein at least one of said criteria is based on a non-linear function of a descriptor value.

8. A computer-aided method according to Claim [2] 1 further comprising the step of deriving one or more criteria associating descriptor values with activity, said criteria including at least one static criterion and at least one dynamic criterion wherein at least one of said dynamic criteria is based on the conformational spaces of a candidate molecule.

9. A computer-aided method according to Claim [2] 5 or Claim 8 wherein at least one of said dynamic criteria is based on a shape descriptor derived from a 3D autocorrelation vector (3D-ACV) of the candidate molecule.

10. A computer-aided method according to Claim 5, Claim 8 or Claim 9 [claim 2] wherein the static criteria are based on physiochemical and topological descriptors at least some of which are chosen from the [descriptors cited in Table II] following descriptors: Molar Mass; Ellipsoidal Volume; Molecular Volume; Molar Refractivity; Lipophilia (LogP); Kappa 1; Kappa 2; Kappa 3; Kappa Alpha 1; Kappa Alpha 2; Kappa Alpha 3; Flexibility; Kier Chi V4; Randic Index; Balaban Index; Weiner Index; Sum of Condition E; Dipolar Moment; Number of C Atoms; Number of O Atoms; Number of N Atoms; Number of H Atoms; Total Number of Atoms; Number of Methyl Groups; Number of Ethyl Groups; Number of Amino Groups;

Number of Hydroxyl Groups.

18. A computer-aided method for the provision, identification and description of molecules exhibiting immunomodulatory activity [, employing] comprising;

a step of molecular modeling [modelling] in which molecular descriptors of a molecule having immunomodulatory activity are determined computationally;[,]

a step of building a combinatorial library using said molecular descriptors and including molecules having said immunomodulatory activity; [and]

a step of selecting candidate molecules which are potentially immunomodulatory; [molecules,]

[wherein said method includes] a filtering step whereby [the] candidate molecules are filtered using [a] at least one static filter representing a plurality of said molecular descriptors; and

a further filtering step whereby candidate molecules are filtered using at least one dynamic filter representing constraints of conformational variations which each candidate molecule must satisfy in order to exhibit said immunomodulatory activity.